Page 96, lines 7-29

05

1,3-Dihydroxy compounds can be synthesized by several well known methods in literature. Aryl Grignard additions to 1-hydroxy propan-3-al give 1-aryl-substituted propan-1,3-diols. This method will enable conversion of various substituted aryl halides to 1-arylsubstituted-1,3-propane diols (Coppi, *et al.*, *J. Org. Chem.*, **1988**, *53*, 911). Aryl halides can also be used to synthesize 1-substituted propanediols by Heck coupling of 1,3-diox-4-ene followed by reduction and hydrolysis (Sakamoto, *et al.*, *Tetrahedron Lett.*, **1992**, *33*, 6845). Substituted 1,3-diols can be generated enanatioselective reduction of vinyl ketone and hydoboration or by kinetic resolution of allylic alcohol. Variety of aromatic aldehydes can be converted to 1-substituted-1,3-diols by vinyl Grignard addition followed by hydroboration. Substituted aromatic aldehydes are also utilized by lithium-t-butylacetate addition followed by ester reduction (Turner., *J. Org. Chem.*, 1990, *55* 4744). In another method, commercially available cinnamyl alcohols can be converted to epoxy alcohols under catalytic asymmetric epoxidation conditions. These epoxy alcohols are reduced by Red-Al to result in enantiomerically pure 1,3-diols (Gao, *et al.*, *J. Org. Chem.*, **1980**, *53*, 4081). Alternatively, enantiomerically pure 1,3-diols can be obtained by chiral borane reduction of hydroxyethyl aryl ketone derivatives (Ramachandran, *et al.*, *Tetrahedron Lett.*, **1997**, *38* 761). Pyridyl, quinoline, isoquinoline propan-3-ol derivatives can be oxygenated to 1-substituted-1,3-diol by N-oxide formation followed by rearrangement in acetic anhydride conditions (Yamamoto, *et al.*, *Tetrahedron*, **1981**, *37*, 1871). Aldol condensation is another well described method for synthesis of the 1,3-oxygenated functionality (Mukaiyama, *Org. React.*, **1982**, *28*, 203). Chiral substituted diols can also be made by enantioselective reduction of carbonyl compounds, by chiral aldol condensation or by enzyme promoted kinetic resolution.

Page 110, lines 25-27

06

Prodrugs of 2-substituted-1,3-amino alcohols or 2-substituted-1,3-diamines are synthesized by following coupling procedures as described in example 1 or example 2 (step A and B) or example 3 (step B) or example 4 depending on the parent compound.

Page 122, lines 3-8

07

Methods: The choice of cell line is dictated by the known toxicity profile of the parent compound. If the toxicity profile of a parent compound is unknown, a panel of different cultured cell lines can be tested. Cells are exposed to a range of prodrug and parent compound concentrations for hours to days. Viability is measured by Trypan blue exclusion, enzyme marker leakage, incorporation of labeled thymidine into DNA or other standard method.

Page 124, lines 19-26

08

Methods: Rats are treated with dexamethasone (50 mg/kg, intraperitoneally) for 4 days as described (Brain EGC et al 1998, Br. J. Cancer 7: 1768). Other CYP-inducing agents such as Phenobarbital or rifampicin may also be used. The induced animals are then administered prodrug orally or systemically and serially sacrificed at various time points. Livers are removed and homogenized in perchloric acid (10%). Following clarification by centrifugation and neutralization, MPO_2-(NHR^{6-}) and/or its metabolites in the homogenates are quantified by standard HPLC methods. A similar study is conducted in uninduced animals.